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ADRENAL CORTEX

John Nichols, M.D.

1910

GENERAL

Embryology and Fetal Zone

The adrenal cortex arises, in the embryo, from the intermediate cell mass (lateral plate mesoderm). At about the 10-mm. stage of gestation (35 days) a wave of cells migrates from the somatopleure to a position at the root of the mesentery. These cells are destined to form the ***fetal***, or ***transitional zone***, first described by Starklowna and Wegrezynowski.[1] During fetal life this zone accounts for the most of the gland's bulk. As the first wave of cell migration (12 mm. or 45 days) is being completed a second wave of cells from the same general somatopleure area migrates to envelop the first cluster forming the outer subcapsular layer. These cells constitute the definitive part of the fetal gland which ultimately becomes the cortex in adult life. Immediately after birth the fetal zone undergoes physiologic atrophy. The event(s) causing or permitting this atrophy are unknown. It is definitely related to birth because adrenals of premature infants begin to atrophy at birth and the rate is the same as in term infants. In postmature infants the fetal cortex does not begin involution until actual birth, whereupon atrophy proceeds at the expected rate. Since the atrophy proceeds in the presence of presumably normal amounts of adrenocorticotropic hormone (ACTH) from the infant's own pituitary, it appears obvious that absence of postnatal ACTH is not the etiologic factor. This atrophy cannot be inhibited by administration of exogenous porcine ACTH. How this fetal zone grows and is maintained during intrauterine life is an enigma. In cases of anencephaly, the fetal zone is formed normally but undergoes atrophy after the 5th month of gestation[2] (Fig. 9.1*A*), even in those few cases of anencephaly with a normal volume of pituitary tissue (Fig. 9.1*B*).[3] One of the suggestions has been that some special trophic substance is present during fetal life, but not after delivery[4]. A special fetal zone adrenocorticotrophic hormone ("FZACTH") may be formed in the central nervous system only during fetal life or perhaps the fetal pituitary under influence of an intact hypothalamus may form an ACTH with unusual amino acid sequence.

We need not dwell on the histology of the fetal gland because the reader can easily observe that the definitive layer beneath the capsule is composed of cells of moderate size sharply demarcated and with good affinity for the usual H&E dyes. The nuclei stain prominently basophilic with a sharp membrane; the cytoplasm stains light purple. Because of its peripheral position this layer of cells although only 1- to 2-mm. thick constitutes about 30% of the cortex of the fetal gland.[4]

The cells of the fetal zone which consti-

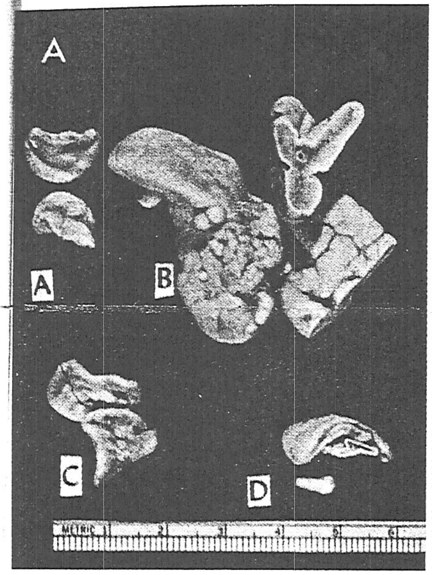


FIG. 9.1A. *A*, adrenals from normal fetus of 5 months' gestation; combined weight 0.70 g. *B*, adrenals from normal term fetus; combined weight 9.60 g. *C*, adrenals from premature anencephalic fetus of 5 months' gestation; weight 0.63 g. *D*, adrenals from anencephalic fetus at term; weight 0.45 g. (From Nichols, J., A. M. A. Arch. Path., *62:* 312, 1956.)

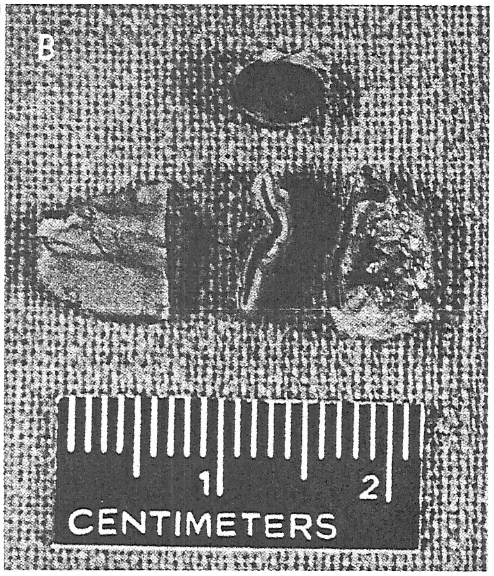


FIG. 9.1B. In this case from an anencephalic at term the pituitary gland at the top consists entirely of normal anterior lobe tissue with vascular stasis. It weighs 90 mg., being the greatest amount of pituitary tissue in anencephaly known to the author. Adrenocorticotropic hormone assays were not done. The adrenal beneath shows atrophy characteristic of anencephaly. (Courtesy of Dr. David Jenkins. From Nichols, J., *An Introduction to Clinical Neuroendocrinology*, Eörs Bajusz, editor, S. Karger, 1967.)

tutes the remainder of the gland are larger than those of the definitive zone. They stain poorly with all techniques, especially H&E. The cytoplasm takes a very pale pink stain and the nucleus a very light basophilic color. Sudan stains reveal that this zone has little lipid. Immediately after birth the fetal zone contains widely dilated vascular channels which, in most instances, are engorged with red blood cells. Within a day or so the cells of the fetal zone begin to break up with loss of cytoplasm and nuclear detail; the vascular engorgement becomes more profound and takes on the appearance of hemorrhage. Hemosiderin, phagocytosis and evidence of regeneration are usually absent. Many seemingly normal infants succumb during this early postnatal period without adequate anatomical cause being found despite diligent autopsy. In many of these infants the prosector reports "hemorrhage of the adrenals" which attending physicians accept as an adequate explanation for death. Examination of these adrenals almost always reveals that the "hemorrhage" is restricted to the fetal zone, the definitive zone being spared. This "hemorrhage" is physiologic and therefore not involved in the death process. By the 4th month of life the fetal zone is 90% atrophic having served no apparently useful function after birth. This concept is supported by the fact that anencephalic infants, without a fetal zone, occasionally live 2 and 3 weeks, to die, apparently, of respiratory failure and malnourishment. It is also well recognized that the crisis in the "salt-losing" form of congenital adrenocortical hyperplasia is usually delayed until 4 to 5 days after birth. Presumably by that time the appropriate adrenocortical hormones from maternal origin are depleted and the infant's failure to form its own hormones becomes evident.

It is most important not to confuse the fetal zone of the human adrenal with the so-called "X" zone of the mouse adrenal cortex, about which there is an extensive literature. The latter appears in the juxtamedullary region about 21 days after birth. It disappears in the male at about 45 days of age simultaneous with appearance of androgens from the testes; it persists in the female until the senile ovary begins to make androgens at about 200 days. Involution begins at the first pregnancy when some androgens are produced. The "X" zone can be maintained for a long period in either sex by gonadectomy and can be made to disappear at any time in either sex by administration of androgens. Quite clearly the "X" zone of the mouse is related to androgens and is not be confused with the human fetal zone.[5]

General Morphology

The weight of the normal adult adrenal gland is not firmly established; certainly it is less than the figure of 5 to 8 g. given in many texts. This is because most adrenals obtained at autopsy are from patients whose illnesses have activated the pituitary to release ACTH thereby causing hypertrophy of the gland. Only glands from healthy persons dying suddenly, as from accident, can be used to establish the weight of the normal gland. Another factor is that most autopsies are done by prosectors who have no special interest in the gland so weights stated in such autopsy protocols are unreliable. When it is possible to recover these adrenals after fixation, 1 to 3 g. of fat can be stripped, with patience, from the complex surfaces and folds of the gland. With such attention it is found that each gland of a normal adult weighs 3.5 to 4.5 g. Symington reported a combined weight for normal adrenals removed at surgery of 7 to 8 g. in the female and 8 to 9 g. in the male.[83] Bloodworth reported that the mean combined weight of the adrenals from 351 unselected autopsies was 12.2 g. and the median 11.5 g. Thirty-one cases were selected from this series which were judged to be completely normal and between the ages of 20 and 60 when the patient underwent sudden death due to gunshot wound, automobile accident, etc. The mean combined weight from this group was 9.7 g. for the males and 8.3 g. for the females.[84]

It is sometimes said that the geometric shape of the glands is determined by the size and shape of space available. This is only partially correct. The foldings, fissures and complex surfaces more logically can be due to different growth rates required by the individual zones to achieve the necessary mass relationships of the mature adult gland.[6] A specific mass ratio of the various zones is achieved and maintained homeostatically to provide for adequate rates of production of aldosterone and cortisol.

Of the two glands, the right is more triangular; the left is more elongated or bean-shaped. Each gland may be divided into three parts, *viz.*, a centrally located head, body and tail. The head contains most of the medulla, the corticomedullary ratio is 4:1; the body contains a small amount of medulla, the corticomedullary ratio being 15:1; while the tail, the lateral most part of the gland, consists entirely of cortex. The anterior portion of each gland is flat and contains a shallow ***anterior groove*** from which emerge the adrenal veins. On the posterior surface there is a ***crest*** or ridge-like elevation flanked by two wing-like portions, the ***alae***.

Vasculature

About 50 or so arteries derived from the aorta and the phrenic and renal arteries supply each gland. These arteries ramify over the surface of the gland and penetrate the capsule forming a subcapsular plexus from which straight capillaries with few interconnecting bridges penetrate the zona fasciculata to form a rich plexus in the zona reticularis at the corticomedullary junction. This vascular plexus is drained by relatively few channels which pass into the medulla. There exists at the corticomedullary junction a type of portal circulation or an area which, at times, may have stagnant flow and on occasion may even flow backward through emissary veins to the surface.

As the tributaries of the veins to and through the medulla merge, they bring with them a collar or cuff of cortical cells. Only in the head region do small muscular venous radicles lie free in medullary tissue without a cortical sleeve. The walls of the central vein in the head of the gland are composed of longitudinal smooth muscle fibers which are much thicker on the posterior side facing the crest (or on that segment of the vein wall facing the medulla). This has been referred to as *medullary tropism* by Dobbie and Symington.[7] These workers believe that contractions of these muscular pillars result in stagnation of blood in the juxtamedullary sinuses thereby exposing the cells of the inner zona fasciculata and zona reticularis to ACTH. This stimulus, in their opinion, accounts for the focal depletion of lipids that progresses from the zona reticularis outward under ACTH stimulation. Parenthetically it may be said that adrenal blood flow does vary considerably from time to time presumably regulated by some neuromuscular mechanism. Also ACTH will triple the blood flow through the dog adrenal within 10 minutes after injection. Dobbie and Symington also believe that in some adenomas the vascular pattern is not arranged in the usual fashion which may account for their nonfunctional status *in vivo*. Yet slices from these adenomas do form steroid hormones when exposed to ACTH *in vitro*.

Zones of Cortex

The terms zona glomerulosa, zona fasciculata and zona reticularis were first used by Arnold[8] in 1866 and were arrived at entirely by observing the patterns of supporting reticulum. Details of the parenchymal cells were not considered. The zona glomerulosa was said to have balls of cells contained in spheres of fibrous tissue; the zona fasciculata was described as parallel sheets of fibers which separate vertical columns of cells; the zona reticularis was considered to be formed of sheets of fibrous tissue arranged in an interlocking pattern like cardiac muscle.

In the human, Elias and Pauly[9] described eight histologic types of cortex (practical significance unknown) based on the arrangement of cells and fibrous stroma of the zona glomerulosa. In general, the cells of the zona glomerulosa are rounded and smaller than the polyhedral cells of the zona fasciculata and have less lipid than the cells of the zona fasciculata. The zona fasciculata cells are polyhedral with a central nucleus and in cases of sudden death have a foamy cytoplasm with abundant lipid. The cells of the zona reticularis are of two types, a light type identical with those in the zona fasciculata and a smaller "dark cell" with a deeply staining cytoplasm. It is held by some that these dark cells of the reticularis normally manufacture cortisol from cholesterol precursors found in the light cells and cells of the zona fasciculata.

Electron microscopy has revealed that the cords of the adrenal are continuous from the "corkscrew" glomerular end through a straight portion in the fasciculata to the reticularis where the cords become indistinct as the medulla is reached.[84] Each cord is composed of 10 to 15 cells which are surrounded by a basement membrane outside of which is a network of capillaries. The cells of the glomerulosa have minimal lipid and mitochondria of the classical type with cristae which are plate-like. In the fasciculata there is a large amount of lipid in membrane-bound droplets and mitochondria which contain some plate-like cristae and some small vesicles which seem to "float free" in the mitochondrial matrix. In some cases the vesicles are accompanied by long, rounded structures which have been called "tubules." In the reticularis the cells contain variable amounts of lipid depending on whether they are dark (compact cells with minimal lipid) or light cells (clear cells with much lipid). The mitochondria of the reticularis are of a special kind which are found in all cells concerned with the production of steroids. The mitochondria have a double outer membrane, minimal mitochondrial matrix, and are packed with small vesicles. They are usually referred to as "vesicular mitochondria" (Fig. 9.2). Long and Jones[88] have recently presented a detailed description of the fine structure of the adrenal cortex in man. They report that the cortical cells have a well developed smooth-surfaced endoplasmic reticulum usually taking the form of a network of anastomosed tubules. Rough-surfaced endoplasmic reticulum is not as prominent as the smooth variety, but is better developed in the human adrenals than in the adrenals of most other species except the monkey. They have demonstrated the same variation in mitochondria between zones which was described above, but emphasized the presence of more tubular cristae in the reticularis than are demonstrated in Figure 9.2, which is from a monkey. They define all of the cristae as long and short tubules but their photographs suggest that many of them are vesicular, conforming to the terminology utilized above.

Adrenals are frequently described, on cut section, as having "abundant lipid," showing lipid depletion or showing "focal lipid depletion." The "lipids" of the adrenal cortex consist mainly of free cholesterol, cholesterol esters, triglycerides, phospholipids, etc.[10] All are white in their pure state. The color of the adrenals is due to lipochrome pigments which also collect in other fatty depots of the body. On one hand the adrenal may have considerable stores of lipid and little lipochrome pigments and appear pale; on the other hand the adrenal may have little lipid and large amounts of lipochrome pigment resulting in a deep yellow color. It is apparent, therefore, that the naked-eye description of the "lipoid state" of the adrenal cortex may be meaningless, and histologic examination may be required.

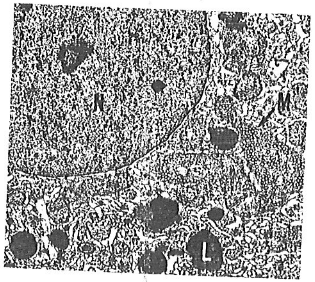


FIG. 9.2. Electron micrograph of parenchymal cell in reticularis of monkey adrenal to demonstrate the vesicular mitochondria (*M*). Also present are portion of the nucleus (*N*) and lipid droplets (*L*). This is a "compact" or "dark" cell because of the paucity of lipid and the large quantity of organelles, especially endoplasmic reticulum, in the cytoplasm. 8500×. (Courtesy of Dr. J. M. B. Bloodworth, Jr.)

A galaxy of elegant histochemical procedures has been applied to the adrenal cortex of the experimental animal and important conclusions regarding corticosteroid formation have been drawn. However, investigations of the human adrenal have been largely disappointing. Simple Sudan stains for total lipids and the Schultz reaction for cholesterol reveal whether or not these substances have been depleted or accumulated in the various zones and locations of the gland in response to ACTH stimulation or to stimulation from the renin-angiotensin system. It is presumed that cholesterol is a precursor or storage form of the various corticosteroid hormones and that when cholesterol (and/or esters) are depleted hormones have been formed and discharged into the blood stream.

Physiology

In considering the adrenal it is quite fashionable to speak or write of "stress." In this context stress of the adrenal *per se* is ambiguous and without meaning. It must be remembered that only two things can stimulate the adrenal cortex. The first is ACTH from the pituitary and the second is renin-angiotensin from the juxtaglomerular apparatus of the kidney. In the sheep it has been demonstrated that alteration of the Na:K ratio may affect the zona glomerulosa. The word "stress" when applied to the adrenal usually means that the patient has had trauma or an illness which has stimulated the hypothalamus and pituitary to release ACTH, to cause enlargement of the adrenal and increased formation of hormones, usually with excretion of storage lipoid.

A dichotomy exists between the function of the inner and outer zones of the cortex. In animals histologic changes limited to the zona glomerulosa and with concomitant changes in the juxtaglomerular apparatus have been repeatedly observed in animals receiving high or low sodium diet or desoxycorticosterone pellet implants. Injection of ACTH elicits changes primarily in the zona fasciculata and reticularis but they may also extend to the zona glomerulosa. Similar changes have been observed in human adrenals. The best evidence that the zona glomerulosa is almost completely independent of the pituitary and secretes aldosterone is the fact that after hypophysectomy the inner zones of the cortex atrophy and the patient shows all of the effects of cortisol deficiency. However the zona glomerulosa atrophies only slightly and aldosterone secretion continues approximately normally while secretion of cortisol is reduced almost to the vanishing point. Quite obviously there is not a sharp "all-or-none" separation of function of the two zones but rather a slight overlapping. Microscopic examination from a hypophysectomized person's adrenal sometimes suggests that the zona glomerulosa and capsule are thickened. This is because the zona glomerulosa and capsule are peripheral. When the zona fasciculata and zona reticularis atrophy the outer zones "cave in" even without much atrophy. Since their mass decreases relatively little and they cover a smaller mass (medulla) their apparent thickness increases.

CONGENITAL LESIONS

Embryonic

The gland has rarely been reported absent without accompanying abnormalities.[11] It has been reported atrophic in cases of agenesis or hypoplasia of the pituitary.[12] Ectopic adrenal tissue may be found in the liver, alongside the mesentery and aorta, in the inguinal canal and in the gonads, especially the testicle. Even in these aberrant locations the gland apparently functions somewhat normally. Wilkins[13] mentions two patients with adrenogenital syndrome arising from adrenal tissue in the scrotum and beside the spermatic cord. These regressed with cortisol administration. The formerly widely held idea that clear cell hypernephromas of the kidney arose from ectopic adrenal tissue has now largely been abandoned, although true adrenal rests are found in the kidney. An adrenal gland has been reported in the cranial cavity in a single instance.[14] Figure 9.3 (*a* and *b*) shows a "horseshoe" adrenal.

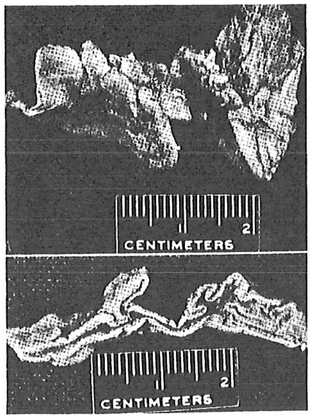


FIG. 9.3. *A*, "horseshoe adrenal" from girl age 5 months with meningomyelocele and fatal septicemia. Both glands are connected by an isthimus passing behind the aorta thereby forming a groove between the two glands. (Courtesy of Dr. Robert Druet.) *B*, section in the horizontal plane reveals normal cortex on both sides of normal medulla which connects the medulla of both glands. No microscopic abnormalities were noted and the pituitary was normal.

The most frequent congenital abnormality is the atrophy regularly found in cases of anencephaly, hydrocephaly and microcephaly. Anencephaly, recently reviewed,[4] has an unusual geographic distribution with a reported instance of 1:600 births in Ireland and 1:50,000 in Lyons, France. Apparently a genetic factor as well as environmental factor are involved in the etiology. It is suggested that minor illnesses such as influenza, herpes, etc., may be causative during the early months when the brain is undergoing complex embryologic folding. Elliott and Armour[15] first described the very small adrenals in anencephaly in 1911, 1 year after the Polish workers Starklowna and Wegrzynowski[1] had described the fetal zone. Speculation tended to ascribe the atrophy to absence or, at least, malfunctioning of the fetal pituitary. Then Meyer[16] in 1912 reported normal adrenals in an anencephalic fetus of 5 months gestation. This suggested that the defect is one of atrophy after the 5th month and is not an agenesis. Unfortunately, Meyer's paper has been largely overlooked. After exhaustively sectioning the sella of 28 anencephalics Angevine[3] in 1938 found pituitary tissue in all. In many instances the tissue was in very small scattered foci of cell clusters. This writer has found ACTH present in tissue from the sella in all of five anencephalics in which it was sought. Because some of the tissue was used for microscopic examination and considerable mesenchyme was included in the material extracted for assay it was impossible to quantitate the amount of ACTH present. Figure 9.1*B* shows the characteristic atrophic adrenals in a case of anencephaly in which a pituitary weighing 90 mg. was found. This pituitary was histologically normal apart from vascular engorgement and is the largest pituitary associated with anencephaly known to the writer. The pituitary of the normal newborn weighs 60 to 80 mg. It has been suggested[4] that the intact hypothalamus either produces a special FZACTH "fetal zone adrenocorticotrophic hormone" after the 5th month of gestation to directly stimulate growth and function of the fetal zone, or that it forms a special humor which stimulates the pituitary to form a special FZACTH. Because atrophy of the fetal zone has been reported in newborn infants with normal hypothalami and deficient pituitary, it is likely that the fetal hypothalamus stimulates the fetal pituitary to form the special fetal zone ACTH. Such stimuli would be absent in cases of anencephaly thereby allowing the fetal zone to atrophy after the 5th month. In Figure 9.1*A*, the naked eye appearance of normal adrenals from an abortion at 5 months of gestation compared with normal adrenals of an anencephalic fetus of 5 months' gestation (*C*) is shown. The small adrenals in a term anencephalic infant (*D*) may be contrasted with the large adrenals of a normal term infant (*B*). Nodules on these full-term adrenals are entirely normal. Figure 9.4 shows a histologic section of an atrophic adrenal.

1911

This experiment of nature, atrophic adrenals and deficient pituitary, provides an excellent opportunity for alert observers to gather important endocrinologic information. For example, it has been found that the 3:1 maternal:fetal ratio of cortisol characteristic of normal pregnancy prevails in cases of anencephaly.[17] This, taken with the fact that the fetal zone is 99% atrophic, suggests that the fetal zone does not form cortisol. The fact that two anencephalic infants surviving 3 and 4 days secreted cortisol at a "low normal" rate despite 99% atrophy of the fetal zone and about 75% atrophy of the definitive zone attests to the efficiency of the remaining definitive cortex.[18]

This atrophy in anencephaly affords an important clue to the function of the fetal zone, a matter hitherto entirely one of speculation. Ten Berge[19] and later Fransen and Stakeman[20] found that women prior to delivery of anencephalic fetuses, excrete an amount of urinary estrogens, especially estriol, only slightly above the nonpregnant level. This suggests that the fetal zone may form or participate in the formation of estrogens. Fransen and Stakeman[21] implanted material from therapeutic human abortions into three groups of immature spayed mice. One group received minced fresh adrenal tissue. Because it is known that the placenta also can form estrogens, the second group was injected with minced placenta while Group 3 was injected with both adrenal tissue and placenta. Only the group injected with both placenta and adrenal tissue showed estrogen effect on the vagina. This indicates that the fetal adrenal forms a precursor which the placenta converts into estrogens. This precursor is dehydroepiandrosterone, a substance previously known to be deficient in plasma of anencephalic infants.[17] Fransen and

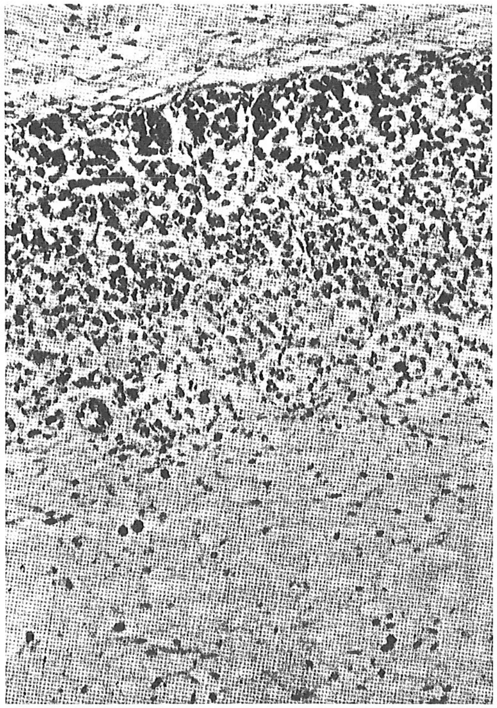


FIG. 9.4. Section of adrenal from a case of anencephaly showing the entire cortex to consist of deeply staining cells similar to those which persist to form the definitive cortex in the normal gland. The inner space adjacent to the medulla is devoid of fetal cortex and is formed of edematous loose mesenchyme. H&E, 190×. (From Nichols, et al. J. Clin. Endocr. *18:* 444, 1958. With permission of the Endocrine Society.)

Stakeman[21] used whole minced glands for their implants. The experiment needs to be redone using (1) tangential slices of definitive zone and (2) tangential slices of fetal zone, both with placentas from normal infants and with placentas from anencephalic infants.

From the foregoing it is apparent that normal estrogen secretion in pregnancy is dependent upon both normal fetal adrenals and a normal placenta. A deficiency of either, *e.g.*, atrophic adrenals, as in anencephaly, or a moribund fetus or an infarcted or separated placenta will result in a low estrogen secretion. This is the basis for estrogen studies to determine the viability and status of the fetus. In cases of Rh incompatability it appears that the fetal adrenal is large and there is an enhanced excretion of estrogens.[22] It appears that the high titers of estrogens in the pregnant woman are unnecessary because pregnancies with anencephalic infants progress normally apart from the high incidence of polyhydramnios. In anencephalic pregnancies the maternal breast changes are normal and metabolic parameters such as the protein-bound iodine and thyroxine-binding globulin are of the expected increased magnitude, yet the patient is excreting estrogens at a rate very slightly above that of a nonpregnant woman. These changes were formerly attributed to increased estrogens. Even if high estrogen values are not necessary for the progression of a normal pregnancy they do afford a convenient index for the status of the placenta and the fetus and its adrenals. Other possible endocrine functions of the definitive and fetal zones of the adrenal are uncertain despite the vast literature of pharmacologic enzyme studies done on tissue slices, *in vitro*.

Congenital Hyperplasia

Congenital adrenocortical hyperplasia (adrenogenital syndrome) is a very rare disorder with an incidence variously estimated at 1:14,000 to 1:40,000 births. Adrenal gross and microscopic studies are inadequate but the etiology—a biochemical one—has been exhaustively studied.[23] Normal formation of cortisol is prevented by an enzymatic defect which is a simple autosomal recessive characteristic. When each parent carries the trait, the incidence among the offspring is therefore 1:4.

In the latter half of pregnancy the normal fetal adrenal begins to secrete steroid hormones including cortisol and an early feedback mechanism is established with the fetal pituitary. When cortisol production is inadequate due to the biochemical defect the fetal pituitary elaborates excess ACTH to stimulate the adrenal resulting in a vicious cycle causing adrenal hypertrophy, (usually referred to as "congenital adrenal hyperplasia"). When excess cortisol crosses the placenta from hormonal treatment[24] or Cushing's disease in the mother, the infant will be born with atrophic adrenals.[25] The adrenals of newborn infants with this disorder had been inadequately studied prior to 1948-1949 when the mechanism became understood and therapy became available. Now, no infant should die with this abnormality and so further opportunities for anatomical studies of the gland will become quite rare.

The gland of the newborn affected with congenital adrenal hyperplasia is large, weighing 20 to 40 g. as contrasted to the normal weight of 5 to 6 g. The capsular surface has many folds which resemble the gyri and sulci of the brain. This folding enhances the ratio of outer definitive cortex to the inner fetal cortex many times. Histologic studies by planographic methods whereby the amounts of definitive and fetal cortex could be calculated have not been done.

Cortical folding was first recorded in Blackman's[26] gross description of the adrenals from four cases with the disorder. Two of the cases were untreated adults who had been afflicted since birth, the third was an infant who died at 6 days of age and the fourth also an infant who died at 6 weeks. However, in another case, that of a boy who lived to be 3 1/2 years, the folding was not mentioned. Blackman presents three other masculinized cases; two resulted from adrenal adenomas and the third, from a brain tumor. Since his microscopic examination of the adrenals

of all four adrenogenital cases revealed a fetal zone increase in the infants and a reticular zone increase in the adults, he concluded that the excess hormones arose from these zones.

Applying geometric principles previously published[6] and taking into account the reduplicated folds in the cortex it can be shown that in the adrenogenital syndrome infants the magnitude of definitive zone increase is actually greater than that of the fetal zone because it occupies a peripheral position. Microscopically, the thickened fetal and reticular zones were composed mainly of large eosinophilic and fuchsinophilic cells many of which had brown pigment. Some of the cells had two and three hyperchromatic nuclei. No stainable lipid was seen. The definitive cortex was also thickened but otherwise essentially normal.

Clinically, the adrenogenital syndrome may be divided into three major types, viz.: (1) masculinizing, (2) hypertensive and (3) salt losing. The masculinizing form (Fig. 9.5) is most often due to *inefficient* hydroxylation of corticosteroids at the 21 position with the result that only very slight amounts of cortisol and aldosterone are formed and there is a build-up of androgenic precursors. These include dehydroepiandrosterone, androsterone, androstenedione, all of which are excreted as 17-ketosteroids in greater-than-normal amounts together with pregnanetriol. In the hypertensive form synthesis at the C11 position is blocked resulting in formation of 11-desoxycortisone (Reichstein's "S") and desoxycorticosterone, as well as pregnanetriol and the androgens listed above. After a patient has lived a few years under these conditions, hypertension results. The salt-losing form is due to a severe, almost complete block at the C21 position with the result that no cortisol at all is formed and thus the minute amounts necessary for aldosterone to act are not present.[27] This then allows progesterone to act unopposed and potassium is retained. As might be expected the juxtaglomerular cells are hypertrophied in the salt-losing form.[28]

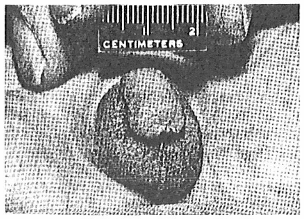


FIG. 9.5. Hypertrophied clitoris in case of 3-week-old female infant with masculinizing adrenogenital syndrome. Such masculinization may be overlooked in a male infant.

The most rare type of this syndrome occurs when there is a deficiency of 3-beta-dehydrogenase and no cortical hormones are formed. This results in a build-up of cholesterol which produces a diffuse "lipoid hyperplasia" invading all cells of all zones in the adrenal. Because there are no cortical hormones the infant (even a male) will be born with female characteristics, in part due to unopposed estrogens from its mother.

The physician should be alert if the mother has previously had an affected infant. Diagnosis of the masculinizing form in the newborn female is usually easy, however, in the male excessive penile growth may not be detected until the child is a few years old. Diagnosis also in the hypertensive form of both sexes may not be achieved until the child is several years old. Diagnosis is achieved by clinical examination of the external genitalia and by finding a high urinary excretion of 17-ketosteroids and pregnanetriol. Diagnosis *in utero* has been achieved in one instance by finding high pregnanetriol values in the amniotic fluid drawn before delivery.[29]

There is a distinct group of cases apart from those mentioned above in which enzyme deficiencies do not become apparent until late childhood or early adult life. Hypertrophied hyperplastic adrenals almost never become malignant. Figures 9.6 and 9.7, however, show an exception.[30] The patient was a male, 8 years old, masculinized since birth, who was cushingoid,

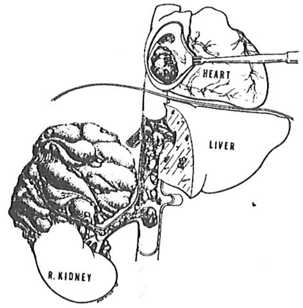


FIG. 9.6. Diagram of invasive adrenocortical carcinoma arising in right adrenal in a case of adrenogenital syndrome. The drawing shows the tumor growing down an aberrant vein into the right renal vein, which it almost occludes, and turning to grow up the inferior vena cava to fill the right atrium as a polypoid mass. The tumor has grown retrograde to fill the hepatic veins and infarct the liver. Microscopic examination revealed, in addition to the extensive thrombus, the tumor to be invading the walls of the vessels in which it is contained, including the right atrium.

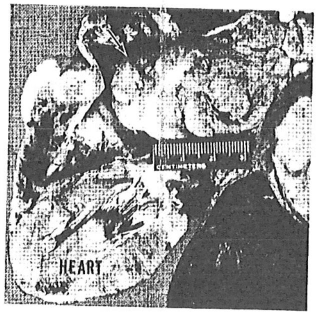


FIG. 9.7. The photograph shows the dense hard tumor diagramed in figure 9.6 with minimal adherent blood clot, filling the right atrium (*arrow*). This is a most unusual method of spread for adrenal carcinoma.

had hypertension, hepatomegaly and ascites. As can be seen, the tumor spread by a most unusual course. Microscopic examination of the tumor at all sites revealed malignant cells growing and attached to vessel walls in addition to the presence of thrombus. Histologic study revealed the tumor to be composed mainly of highly anaplastic cells characterized by marked variation in size and shape with many bizarre nuclei and few mitotic figures. Many multinucleated giant cells and a few "monster" cells were present. Necrosis was prevalent and only a few areas were present which contained cells that resembled the parent gland. The contralateral (left) adrenal showed profound atrophy of the zona fasciculata and reticularis. The ascites was intensively treated with spironolactone, the effect of which can be seen as intracytoplasmic inclusion bodies in the zona glomerulosa of the opposite adrenal (Figs. 9.8 and 9.9).

The sister of this patient, then age 5, also had been masculinized since birth. She, too, had been treated with cortisol and had become refractory to this therapy. Exploration revealed a 3-cm. spherical right adreno-cortical carcinoma histologically similar to that of her brother. This tumor showed capsular invasion. Exhaustive sectioning of the atrophic left adrenal revealed a single focus of malignant cells occupying the zona fasciculata. (Fig. 9.10). This tumor measured 0.4 mm. in diameter and is the smallest adrenocortical carcinoma known to this writer.

ACQUIRED LESIONS

Tumors and Hypertension

Since Conn's report[31] in 1955 of ***"Primary Aldosteronism"*** resulting from an adenoma of the adrenal cortex the designations of "hypertrophy," "hyperplasia," "adenoma" and "nodule" have become of paramount importance. The increasing misuse of these terms in the clinical literature warrants their definition. ***Hypertrophy*** is the increase in gland size due to increase in cell size. It is caused by ACTH stimulation from the patient's own pituitary or from

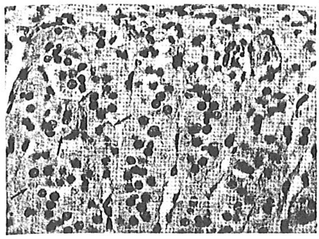


FIG. 9.8. Photomicrograph of zona glomerulosa of left atrophic adrenal showing cytoplasmic inclusion bodies (*arrows*) first described by Janigan[81] in patients treated with spironolactone. These bodies are mainly phospholipid in nature and must be result of the drug on the zona glomerulosa. H&E, 285×.

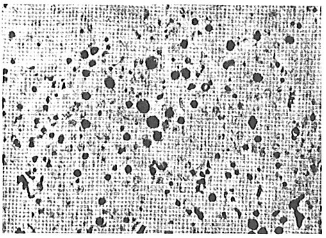


FIG. 9.9. Photomicrograph of same zona glomerulosa as in Figure 9.8 showing variation in size of the dark-appearing bodies and lamination of the larger ones. Sudan black stain, frozen section, 285×.

an ACTH-producing tumor (***e.g.***, lung carcinoma), or it may be iatrogenic. Usually the zona fasciculata and zona reticularis hypertrophy and all three dimensions of the gland are involved, not just the two observed in the single plane of the microscope. Hypertrophy of the zona glomerulosa has been described as due to excess renin-angiotensin from hyperplasia of the juxtaglomerular apparatus. ***Hyperplasia*** is the increase in number of normal cells composing the gland. If hyperplasia is diffuse it must result from an increased amount of circulating ACTH; if hyperplasia is localized the hyperplastic cells are independent of ACTH and are functioning autonomously. An ***adenoma*** is a localized circumscribed group of benign cells which may be either hypertrophic or hyperplastic. These cells may have morphologic characteristics different from the surrounding normal cells or they may be identical. The adenoma may be visible to the naked eye or so small that it can be detected only with the microscope after histologic preparation. It frequently has a fibrous septum setting it apart from the normal surrounding parenchyma which may be compressed by the adenoma. Sometimes the adenoma would escape detection if shrinkage and other artifacts of histologic processing did not make it apparent (Fig. 9.11). A single definition of a ***nodule*** has not been accepted. Many persons use the terms "nodule" and "adenoma" interchangeably. This gives rise to confusion. This writer reserves "nodule" for the small spherical excrescences of cortical tissue appearing on the capsular surface and projecting into the surrounding fat as can be seen on the surface of the gland in Figure 9.1*b*. Some nodules are attached to the capsule by a pedicle and others exist as independent islands in the surrounding fat.

In cases where both glands are uniformly and diffusely enlarged from hyperplasia and/or hypertrophy, it is presumed that the cause is increased plasma ACTH from the pituitary or from an ACTH-producing tumor of nonendocrine source. Microscopic examination of the enlarged adrenals may show them to be normal and the patient may or may not have clinical signs of hypersecretion. It is impossible, on gross examination of adrenals, to ascertain their functional output; however, if the gland is atrophic one may suspect that the gland is in a state of hypofunction. Detailed microscopic examination of the nuclei of glands from patients with Cushing's syndrome or ACTH administration may reveal the nuclei to be large but after hypophysectomy they will be small.[32] If one gland

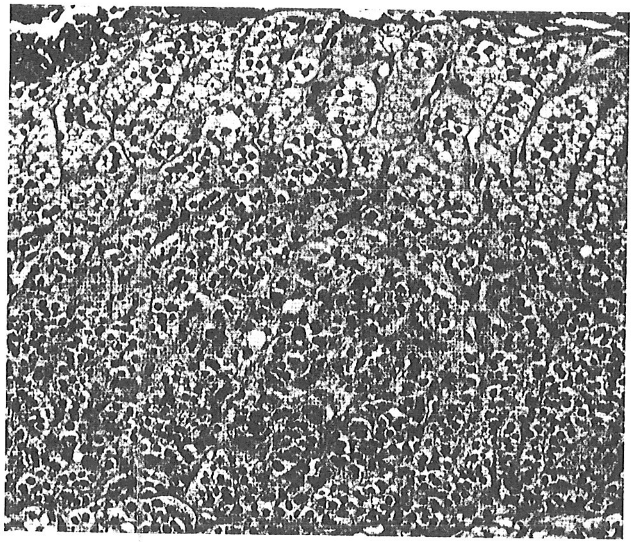


FIG. 9.10. Photomicrograph of tumor in left adrenal of sister of patient depicted in Figures 9.6 to 9.9, age 5 with adrenogenital syndrome. The atrophying effects of substitution therapy on the zona fasciculata can be seen in the lateral margins while the zona glomerulosa is intact. In its largest measurement the tumor had a diameter of 0.4 mm. The pleomorphic cells of the zona fasciculata have lost their polarity and are growing faster than the normal cells to produce a nodule without apparent invasion. Multinucleated cells and cells with giant nuclei are seen. H&E, 275×.

is atrophic and the alternate gland large or normal in size the conclusion is that the alternate gland is autonomous and is hypersecreting cortisol causing the pituitary to diminish secretion of ACTH. The alternate, hypersecreting gland may be "normal" to the naked eye and microscopic examination. Most often, however, it contains an adenoma large enough for the surgeon to recognize, in which case the remaining parenchyma of this gland may also be atrophic with characteristic thin edges. When this condition prevails the adenoma is autonomous and potentially malignant.

Many patients, clinically normal, harbor surgically palpable adenomas which have no effect on the contralateral gland or normal cells of the ipsilateral gland. Microscopic examination may reveal the adenoma to be composed of normal cortical cells, cells with only subtle changes, or cells frankly different from normal. Of course a large alternate gland may be malignant with or without invasion and/or metastases.

The adrenal cortical etiology of the hypertension in Cushing's disease is accepted by all and most have agreed that the cortex is in some way associated with "essential" hypertension, at least in a permissive role. Prior to Conn's report,[31] the aldosterone capacity of some adenomas was not suspected. Adenomas are found with surprising frequency in routine hospital autopsies but the prosectors do not correlate them with Cushing's syndrome, hence the term "incidental, nonfunctioning adrenal cortical adenomas." Conn[33, 34] takes pathologists to task for this designation despite the fact that prior to 1955 primary aldosteronism was unknown. But simultaneously he does quote two excellent studies by pathologists whose findings support his own thesis. Russi and associates[35] and Reinhart and associates[36] reported a statistical correlation between adrenal cortical adenomas and hypertension prior to identification of aldosterone and elucidation of its role in producing hypertension. Numerous other studies revealed the adrenals of "essential hypertensives" to be large and it has been suggested that the zona glomerulosa, site of aldosterone production, is disproportionally increased in mass in such cases.

Recently Conn and associates[37] after examining 103 patients, have set forth their criteria for "primary aldosteronism," in patients without renal disease and not recently treated with chlorothiazide, as listed in Table 9.1.

A cure or profound amelioration of symptoms follows removal of the tumor, or adrenal containing the tumor. Inasmuch as the adenoma is secreting aldosterone it is logical to assume that the tumor arises from cells of the zona glomerulosa and, also, that the uninvolved portion of this

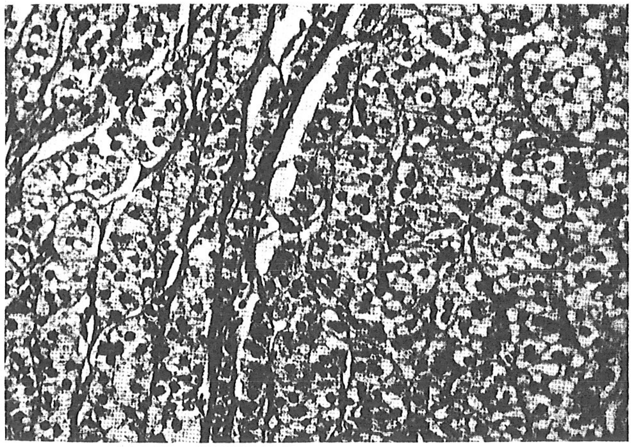


FIG. 9.11. Photomicrograph of an adenoma, not apparent on naked-eye examination, of a freshly cut surface of an adrenal cortex. The cells of the adenoma on the *right* are almost identical with those composing the zona fasciculata on the *left*. Only the cleft produced by histologic manipulation makes the adenoma apparent. This is due to different rates of shrinkage and tension incident to fixation, embedding, cutting, staining and mounting the tissue. H&E, 340×. (From Nichols, J., J. Clin. Endocr., *26:* 550, 1966. With permission of the Endocrine Society.)

TABLE 9.1

Primary aldosteronism

Symptoms	%	Findings	%
Muscle weakness	73	Hypertension	100
Polyuria (nocturia)	74	Retinopathy	50
Headache	51	Cardiomegaly	41
Polydipsia	46	Trousseau sign present	17
Paresthesia	24	Tetany	9
Visual disturbance	21	Chvostek sign present	9
Intermittent paralysis	21	Paralysis	4
Tetany	21		
Fatigue	19		
Muscle discomfort	16		
No symptoms	6		

Biochemical Alterations

- (A) Blood
  - Hypokalemia
  - Hypernatremia
  - Hypochloremia
  - Hypomagnesemia
  - Alkalosis
- (B) Urine
  - Increased aldosterone excretion
  - Normal 17-ketosteroid and 17-hydroxycorticosteroid
  - Impaired concentrating ability
  - Pitressin resistance
  - Decreased ability to acidify neutral or alkaline urine
  - Decreased renal conservation of potassium
- (C) Body fluids
  - Increased body exchangeable Na
  - Decreased body exchangeable K
  - Low sweat Na concentration
  - Low Na:K of saliva
  - Increased plasma volume
  - Decreased hematocrit
- (D) Electrocardiogram
  - Shows changes compatible with hypokalemia

same zona glomerulosa and that of the contralateral gland would be atrophic. This is usually not the case. The original report[31] in 1955 stated the zona fasciculata of the contralateral gland was atrophic. Subsequently[33, 34, 37] zona glomerulosa is said to be atrophic; however, the poor quality of the accompanying photomicrographs precludes critical appraisal.

Plasma angiotensin activated by renin secreted by the juxtaglomerular cells of the kidney was found to be a potent stimulator for secretion of aldosterone. Secondary aldosteronism is the term applied to the increase of activated angiotensin and aldosteronism found in such situations as passive congestion of a failing heart, pulmonary hypertension, liver failure with ascites, obstructive renal arterial lesions or hemodynamic changes in kidney characteristic of malignant hypertension. Conversely, the increased aldosteronism from a primary autonomous cortical adenoma is accompanied by a decrease in plasma renin activity. Thus hypertension, hyperaldosteronism, hyporeninism and hypokalemia are characteristic of "primary aldosteronism." It is apparent, therefore, that the renin level is a key factor in the differential diagnosis of aldosteronism. This is, unfortunately, a complex determination and is done in only a few laboratories.

In a retrospective study of their cases Conn and associates[34] considered primary aldosteronism the late phase of a disease which a few years earlier would have fit into the diagnosis of essential hypertension. It is now possible to identify patients harboring an "aldosteronoma" in the early stages of essential hypertension, and before the fully developed syndrome of primary aldosteronsim becomes apparent. Renin is assayed in the plasma of patients who have not had antihypertensive therapy, especially chlorothiazides, for a few weeks. Aldosterone is determined in the urine. Patients with aldosteronomas on a normal sodium diet (100 mEq./day) excrete increased amounts of aldosterone, normal amounts of 17-ketosteroids and 17-hydroxycorticosteroids, have normal plasma sodium and potassium values, but have very low plasma renin values. When sodium intake is increased to 250 mEq./day or decreased to 15 mEq./day, aldosterone and renin values do not change. The plasma renin values of these patients remains low 4 hours after assuming the upright position from recumbency. It will be recalled that the normal person on a high sodium diet has a low aldosterone excretion rate and low plasma renin value while on a low sodium diet he has a high aldosterone excretion rate and a high plasma renin value. Also, the normal person has a profound increase in plasma renin values 4 hours after assuming erect posture from recumbency.

This brings us to the ***adenoma*** which occurs predominantly in females in the left adrenal at a ratio of about 2:1. Both Conn and Russi find considerable variation in size of the adenomas with many less than 1 cm. in diameter. Its histologic structure is usually quite similar to that of the normal surrounding cortex with the cells frequently distended by lipids and indistinguishable from those of the zona fasciculata. Measurements by Conn revealed that adenomas causing ***normokalemic essential hypertension*** are smaller than 1.5 cm. in spherical diameter, the average of those causing primary aldosteronism. Amelioration of the symptoms after removal of adenomas as small as 3 and 5 mm. in diameter has been observed by Nesbit.[38] Assuming density of the adenoma to be 1.0 the tissue mass (weight) of these tumors may be calculated from the formula: weight = $^4/_3\pi R^3$. Some comparative weights and measurements are shown in Table 9.2. The foregoing considerations emphasize the difficulties faced by surgeons in dealing with this tumor. It also makes apparent the extreme importance of careful gross and microscopic examination of the gland which, unfortunately, is too often assigned to a resident without special interest in the gland. Perfunctory examination at autopsy has definitely contributed to the lag in acquiring knowledge of the adrenal cortex. When one realizes that the histologic picture of a 3-mm. (14-mg.) tumor which produces profound clinical effects may be identical with a tumor which weighs a kilogram and has extensive metastases, but is without clinical effects, the utter futility of trying to assess the secretory state of the adrenal on microscopic examination is apparent. These 3-mm. aldosteronomas must be among the most active endocrine tissues in the body.

TABLE 9.2

*Adrenal cortical adenomas**

Diameter of Adenoma	Weight of Tissue		Per Cent of Adrenal	Per Cent of Zona Glomerulosa
	g.	mg.		
3 mm.	0.014	14	0.17	0.7
5 mm.	0.065	65	0.8	3.0
1.0 cm.	0.522	522	6.6	23.0
1.5 cm.	1.763	1,763	22.0	88.0

*The table shows the weight in grams and milligrams of spherical adenomas of varying sizes. The percent of adenoma tissue is also shown, assuming the adenoma and cortical tissue both to have the same specific gravity of 1.0, and the adrenal mass to be 8 g. as composed of two normal adrenals of 4 g. each. The corresponding percent of zona glomerulosa is also shown assuming the zona glomerulosa to comprise 25% of the adrenal mass.

The magnitude of the difficulty in assessing the functional and/or malignant status of these cortical adenomas is well illustrated by the left adrenal in Figure 9.12. At time of operation for pancreatic disease by a competent surgeon there was no suggestion of adrenal or pituitary disease and both adrenals were explored and considered normal. Five weeks later at autopsy the left adrenal was found to weigh 12 g. and contain an ovoid adenoma

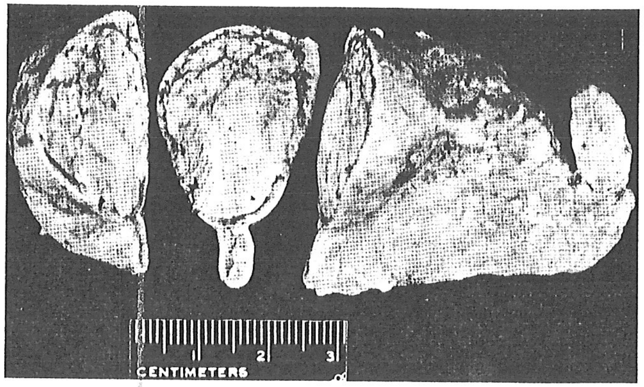
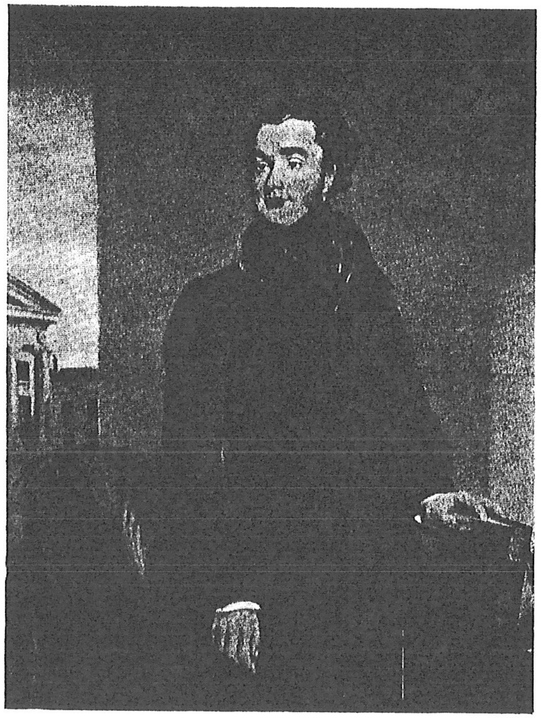


FIG. 9.12. Left adrenal with a nodule at the tail and an "adenoma" in the head and body. The diameters of the adenoma are 2.0, 2.5 and 3.0 cm. with an average of 2.5. From the formula $^4/_3\pi r^3$ the adenoma weighs approximately 6.5 g. Since the total gland weighs 12 g. the uninvolved portion of this gland weighs 5.5 g. as compared to 5 g. for the opposite adrenal. Naked-eye examination of this gland suggests it to be a benign adenoma. (Courtesy of Dr. Larry Welling.)

as well as a nodule on the capsular surface at the tail. The right adrenal weighed 5 g. and appeared normal as did the uninvolved portion of the left adrenal. On sectioning, the yellow cut surface of the adenoma bulged indicating pressure from rapid growth and stretching of the "capsule" which has retracted. No hemorrhage or necrosis was apparent to the naked eye although the parenchyma was soft.

Microscopic examination of the adenoma revealed it to be composed of cells normal in appearance and almost identical with those of the zona fasciculata of the adjacent normal gland. The adenoma had a poor capsule but was well demarcated from the remainder of the gland. The small areas of necrosis in each section of the adenoma, as can be seen in Figure 9.13, indicate extremely rapid growth. The communicating veins of Symington are thrombosed, as seen in Figure 9.14, with organization and intimal proliferation due to stasis and retrograde blood flow caused by this adenoma. Exhaustive sectioning failed to reveal tumor cells in the vessel or thrombus. The necrosis together with cells outside the capsule (Fig. 9.15) and the presumably rapid growth, an opinion derived from the surgeon's report, brings this writer to the diagnosis of malignant adrenocortical carcinoma.

Surgeons put great pressure on pathologists for a quick frozen section diagnosis at the operating table, especially when the tumor is small and without obvious metastases or invasion. This should be resisted because a histological diagnosis in such a situation will not affect the course of the surgery. The diagnosis will be more accurate if the untraumatized gland is fixed, later expertly sliced and photographed so that multiple sections of the capsule with surrounding tissue can be studied for invasion. This 24 hour delay will be of more benefit to the patient and surgeon than an attempt at frozen section diagnosis on very subtle criteria.



THOMAS ADDISON, M.D.

Adrenal Cortical Insufficiency (Addison's Disease)

It is mandatory that a few words be devoted to the good Doctor Thomas Addison. He took his M.D. at Edinburgh in 1815 at the age of 22 with a thesis entitled "De Syphilide et Hydrargyro" and by 1817 had paid his fees to become a "perpetual Physician Pupil" at Guy's Hospital. He devoted himself to Guy's where he reigned supreme by his energetic and inspiring teaching. He remained a bachelor until 52 years of age, never held office in the Royal College of Physicians, was not elected Fellow of the Royal Society and did not receive the accolade as did his contemporaries Astley, Cooper, Gull and Wilks. He wrote only 14 scientific papers and three of these were jointly, one with Bright, one with Gull and one with Morgan. He wrote the first volume of a two volume text book of medicine with Bright but the second volume did not appear. In 1849, 6 years before his monograph, he presented a paper to the South London Medical Society entitled "Anaemia—Disease of the Supra-renal Capsules."[39] This contained a vivid picture of what passes today for pernicious anemia and is the beginning of some considerable confusion. As a dermatologist and general physician his attention was attracted to the unusual bronze pigmentation in some of his patients. He presented two cases before the Royal Medical Chirurgical Society but they were not accepted for publication in the *transactions*. This caused him considerable distress because in 1849 and 1850 he was president of the society. The monograph entitled "On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules"[40] appeared in May 1855 when his age was 62 years. This was the result of the goading of his faithful pupil, Samuel Wilks who had done most of the dissections and possibly much of the writing for it, because Addison was a reluctant author. The monograph contains one case of tuberculous adrenals with skin pigmentation documented by Richard Bright in 1831, the significance of which had not been recognized by Bright. Addison considered that he had found the function of the suprarenals and that they were involved in blood formation and skin pigmentation. He dedicated the monograph to Lord Hawke, Captain of the Yorkshire Cricket Club. This is as if Kendall had dedicated an important paper to Babe Ruth. The monograph was received with mixed reaction, *i.e.*, acceptance on one hand and rejection on the other. During his latter days, emotional turmoil, *e.g.*, suicide attempts, dominated him. He resigned Guy's in 1860 and retired to Brighton where trivial things continued to upset him. He died in 1860 on Friday, June 29, a few months after Richard Bright, leaving an estate of £60,000[41] or $144,000.00 at current rate of exchange but worth considerably more at that time.

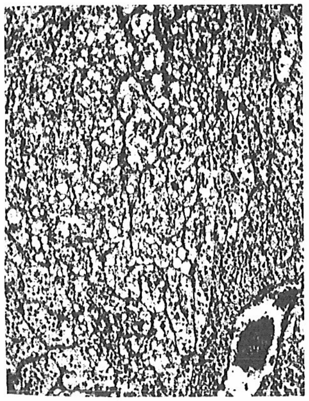


FIG. 9.13. This section of the adenoma reveals necrosis in the otherwise histologically normal parenchyma and indicates the tumor is growing too rapidly for its blood supply. This feature strongly suggests malignancy. H&E, 100×.

Today the disease which bears his name may be characterized by increased skin pigmentation, mucous membrane pigmentation, freckling, vitiligo, loss of weight,

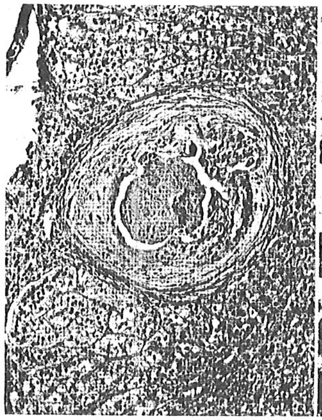


FIG. 9.14. This section from the normal zona glomerulosa of the same adenoma as in Figures 13 and 14 shows one of the communicating vessels of Symington adjacent to the adenoma. The vessel contains a thrombus and shows considerable intimal thickening and proliferation. Exhaustive sectioning failed to reveal tumor cells. Presumably this is due to retrograde blood flow and stasis in this vessel caused by an alteration of hemodynamics by the rapidly growing adenoma. H&E, 100×.

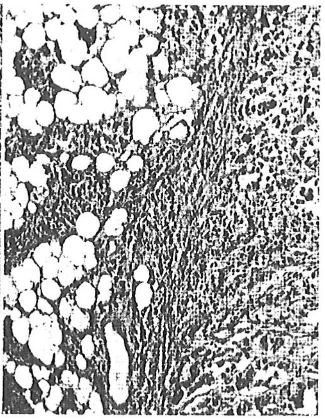


FIG. 9.15. This section from the capsule of the adrenal containing the same adenoma as in Figures 12 to 14 shows apparently benign cells "invading" or growing free in the extracapsular adipose tissue. These cells are free and growing without regard to any organization thereby suggesting malignancy. H&E, 80×.

emaciation, anorexia, vomiting, diarrhea, abdominal pains, muscular weakness, decreased hair growth, loss of pubic hair, loss of libido, weakness, slow cerebration, achlorhydria, nausea, small heart, low blood volume, low blood pressure, low sodium, elevated potassium, normocytic normochromic anemia, low hemoglobin, and low or absent aldosterone, 17-ketosteroid and 17-hydroxycorticosteroid excretion. Pernicious (Addison's) anemia occurs only rarely simultaneously with the adrenal disease.[42]

Adrenal Necrosis

Adrenal necrosis resulting in Addison's disease may be due to:

(a) infection necrosis
(b) cytolysis or "atrophy"
(c) metastatic replacement
(d) infarction necrosis
(e) amyloidosis

Usually 80 to 90% of both cortices are destroyed before symptoms appear. At the time of death in untreated patients, about 5% of the cortex remains which represents the minimal threshold below which a patient cannot maintain adequate homeostasis. A similar situation is created when for therapeutic purposes a surgeon removes an entire gland and $^{9}/_{10}$ of the opposite gland.

1. Infection necrosis of the adrenal is usually visible upon gross inspection as firm, rubbery, yellowish or yellowish-gray areas with a uniform appearance on sectioning.[43] The cause most commonly found is tuberculosis (Fig. 9.16) or less frequently histoplasmosis (Fig. 9.17). The adrenals

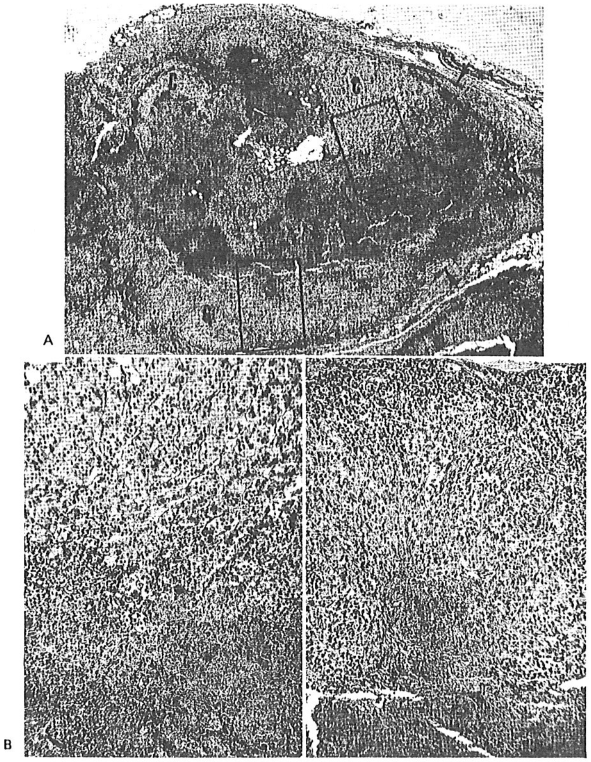


FIG. 9.16A. Dimorphism of inflammatory reaction in largely necrotic tuberculous adrenal gland. Adjacent to cortical remnants (*C*) an exudate of lymphocytes and plasma cells is present without granuloma formation. In contrast, a diffuse granulomatous reaction (*G*) has developed from those parts of the capsule where all viable cortex has disappeared. In transitional zone (*arrows*) lymphocytic infiltration is prominent. PAS-hematoxylin, 19×.

FIG. 9.16B. Transition from adrenal cortex, via lymphocytic exudate to incomplete necrosis. PAS-hematoxylin, 95×.

FIG. 9.16C. Enlargement of granuloma with epithelioid and giant cells which has developed in response to by-now-complete necrosis in those areas where all viable cortex had disappeared. PAS-hematoxylin, 95×. (Fig. 9.16A to C from Frenkel, J. K., *The Adrenal Cortex*, H. D. Moon, editor. Hoeber Medical Division, Harper & Row, Publisher, 1961.)

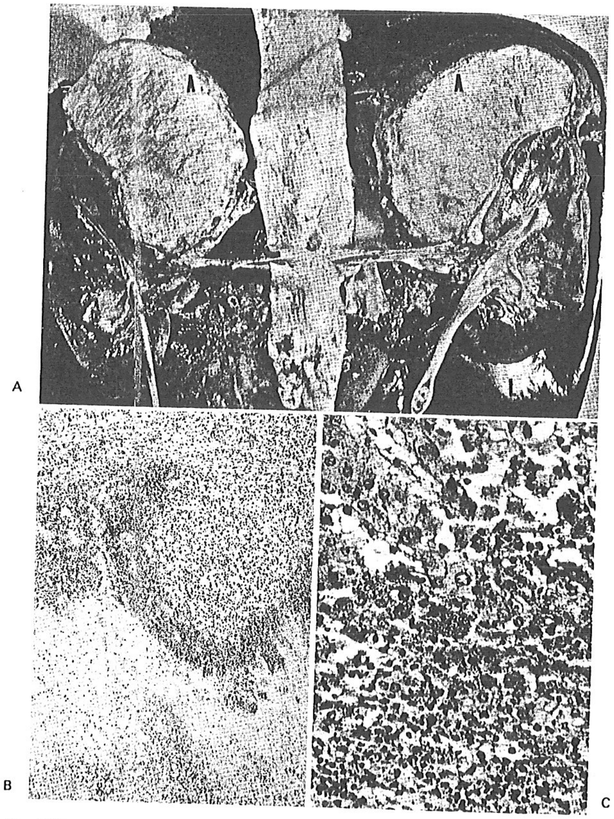


FIG. 9.17A. Massive necrosis of greatly enlarged adrenal glands (*A*) in patient with Addison's disease due to histoplasmosis. Necrotizing process does not extend into kidneys (*K*) or liver (*L*) to which adrenals are adherent. Approximately 5×.

FIG. 9.17B. Adrenal necrosis due to histoplasmosis. Transition from a focus of surviving adrenal cortex to necrosis (*below* and *left*). PAS-hematoxylin, 40×.

FIG. 9.17C. Transition from intact cortex, *above*, to necrosis, *below*. Note numerous Histoplasma organisms and lack of significant inflammatory reaction. Most of the nuclei (*below*) are from necrotic parenchymal cells. PAS-hematoxylin, 264×. (Fig. 9.17A to C from Frenkel, J. K., *The Adrenal Cortex*, H. D. Moon, editor. Hoeber Medical Division, Harper & Row, Publisher, 1961.)

are generally the only, or at least the principal, progressive focus of infection in the body.[44] On histologic examination and in comparison with lesions in other organs, the adrenal lesions show a larger number of microorganisms (Fig. 9.17), more extensive cell necrosis, a minimal granulomatous reaction and no tendency to heal by fibrosis[45] (Fig. 9.16). The area of necrosis is limited by a few lymphocytes, plasma cells and abortive epithelioid cells (Fig. 9.16). The progressive nature of the adrenal foci is well illustrated by a statement concerning 1000 necropsy observations at the Mayo Clinic in which "small areas of healed tuberculous lesions such as those which are found in the lungs, liver and spleen, have not been found in the suprarenal glands."[43]

As mentioned above, the adrenal is infrequently infected with tuberculosis relative to the frequency of infection by this organism in other organs. Oddly, adrenal tuberculosis is accompanied by the most limited extra-adrenal tuberculous lesions and conversely chronic progressive pulmonary tuberculosis is not commonly accompanied by adrenal necrosis. This suggests that the pathogenesis of the two conditions differs. The conditions operative have been obscure since Addison's original description in 1855 of a syndrome consisting of "anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and peculiar change of color in the skin, occurring with a diseased condition of the suprarenal capsules." Addison's cases were mostly a result of tuberculosis. Experimental investigation of this disease has been hindered because tuberculosis in animals rarely if ever gives rise to adrenal destruction.

A suitable model became available during the centennial year (1955) of Addison's description in the form of a protozoan infection of hamster adrenals.[46] This protozoan, *Besnoitia jellisoni,* continues to grow in the adrenals when immunity is acquired, during the 3rd and 4th week of infection, although the lesions regress in the other organs of the hamster. When it was found that the injection of pharmacologic doses of cortisol inhibited the acquisition of generalized immunity, and prevented adrenal infection at the same time, it became apparent that in both hamsters and man endogenous adrenal corticoids interfered with the operation of immune factors within the adrenals. Man and hamsters secrete cortisol as the principal adrenal secretory product[47, 48] in contrast to most rodents. Hence the marked proliferation of microbes resulting in extensive adrenal necrosis, the inhibition of granuloma formation in the adrenal and the defective fibrosis, were attributed to the local hypercorticoid state. In the hamster as in man, healing foci of adrenal necrosis were seen for the first time[45, 49] following corticoid replacement (Fig. 9.18) which was made possible only after the synthesis manufacture of cortisone and congeners in the 1950's.

Selective destruction of the adrenals could be attributed to failure of immunity to be acquired locally, following disseminated acute infection. However, the rare occurrence of adrenal involvement had to be explained otherwise. One reason appears to be the infrequent seeding of the adrenals, without the development of such extensive lesions in other organs that rapid death would have been brought on from miliary tuberculosis involving lungs and meninges. Another is the poor suitability of adrenals as a substrate for tubercle bacilli and Histoplasma, both of which grow much better in lymph nodes. A third is the ability of the adrenals, at least if involved with fungal infection, to undergo compensatory hyperplasia, so that a destructive lesion would not necessarily result in the symptoms of Addison's disease for a long time.[50]

In tuberculous patients, a degree of hypothalamo-pituitary-adrenal hypofunction is present, and compensatory hyperplasia is deficient in the adrenals destroyed by tuberculosis.[50] This is not so in fungal infections, where 30- to 40-fold enlargement has been found.

An understanding of the adrenal infection necrosis mechanism suggests a therapeutic measure, applicable especially if the

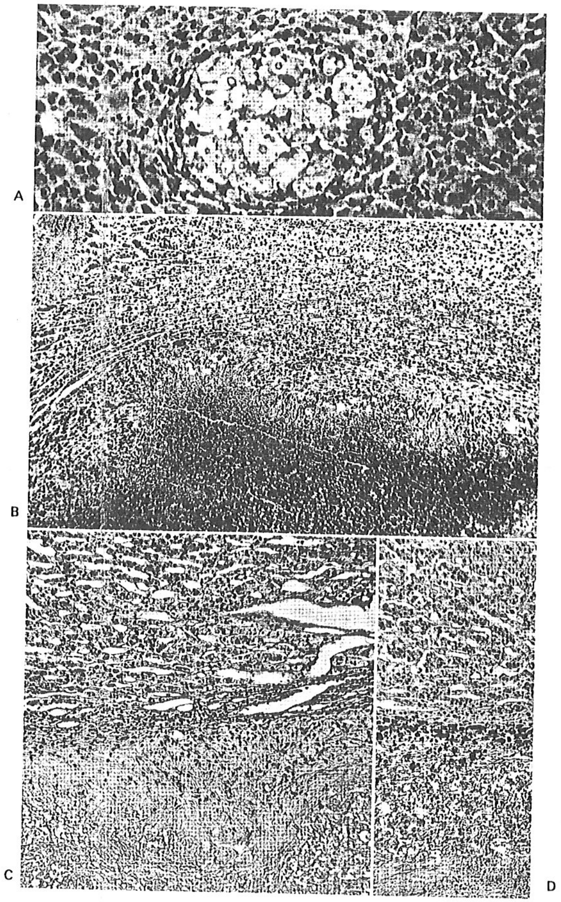


FIG. 9.18A. Cryptococcal focus in adrenal, accompanied by a few lymphocytes and macrophages. This is the typical lesion showing only necrosis. PAS-hematoxylin, 160×. (Courtesy of Dr. Jack H. Hill.)

FIG. 9.18B. Granulomatous reaction with epithelioid and giant cells surrounding focus of adrenal necrosis due to Cryptococcus in patient treated with cortisol. Modification of typical lesion due to adrenal hypofunction. PAS-hematoxylin, 80×.

etiology of the lesion is obscure. Ample replacement therapy, resulting in feedback inhibition of the adrenals, will put any remaining corticoid cells at rest from steroidogeneis, and by decreasing the local tissue hypercorticism will subject the adrenal to the same immune mechanisms operative elsewhere in the body. This would preserve remaining adrenal cells for regeneration after the infection is cured. Specific antimicrobial chemotherapy should of course be started, if available, as soon as an etiologic diagnosis has been made.

2. Adrenal cytolysis or "atrophy." In a series of young military patients with Addison's disease, Friedman[51] found 60% of patients with atrophic adrenals. In the usual mixed population the incidence of this lesion is smaller. Sloper,[52] 1955, encountered only 40%, while in military personnel the lesion accounted for only 22% of cases before World War II.[51] There is little doubt that the increased incidence of adrenal atrophy is due, at least in part, to the decreased prevalence of tuberculosis in the general population.

The adrenals appear atrophic as if destroyed by rapid cytolytic necrosis. Their "contraction" scarring frequently prevented effective compensatory hyperplasia. Histologically, few cortical cells may remain, or individual and nodular hyperplasia may be seen. The medulla is rarely involved. At the time of death, presumably after a course of a few weeks or months, only a few lymphocytes are present in the adrenal. Friedman postulated viral destruction similar to that which occurs in viral hepatitis. In cytomegalovirus infection of man which may selectively (though rarely) affect the adrenals, cellular debris remains.[45] In herpes and varicella infection, destruction is more rapid and could result in the lesions observed. However to date, an etiology has not been established.

Adrenal contraction has also been found in patients with familial mucocutaneous candidiasis followed by Addison's disease.[53] The adrenals are not involved by fungal infection. However, as candidiasis appears to always precede the development of adrenal dysfunction the presence of a toxic fungal factor has been postulated to explain adrenal atrophy, as well as the hypoparathyroidism and sprue-like syndrome developing in many of these patients. An effort to prove this by a prolonged series of injections of Candida into hamsters was unsuccessful, however (Frenkel and Havenhill, unpublished data). The demonstration of a candidacidal substance in normal serum, and its absence in patients with mucocutaneous candidiasis, including those with Addison's disease, has provided a new approach to investigating the series of links involved in this interesting syndrome.[54]

Adrenal antibodies have also been demonstrated in patients with candidiasis and Addison's disease of recent onset, as well as in other patients with adrenal dysfunction alone.[55] The significance of these antibodies, especially whether they are the cause or effect of adrenal destruction, is being investigated. Some investigators hold that many obscure cases may thus be explained.

The frequent association of adrenal atrophy with thyroid atrophy, Schmidt's syndrome,[85] and the occurrence of lymphocytic infiltrations in both organs as well as the demonstration of thyroid antibodies, has led to speculation that both conditions may be due to an immunologic disease, perhaps of autoimmune nature.

3. Metastatic adrenal replacement. This has been observed, especially with a variety of carcinomas metastatic to the adrenal, usually carcinomas of the lung and breast. Willis[56] found 9% of all carcinoma metastases in the adrenals. In rare instances, the tumor (frequently of lung ori-

FIG. 9.18C. Zone of fibrosis surrounding focus of adrenal necrosis due to Cryptococcus in patient treated with cortisol. Arrest of progressive lesion due to adrenal hypofunction. H&E, 80×.

FIG. 9.18D. Intense phagocytosis of apparently nonviable cryptococci by macrophages (dark-staining) in zone of fibrosis, indicative of increased immune potential. Same area as shown in Figure 9.18C. Grocott's methenamine-silver hematoxylin stain, 80×. (Fig. 9.18A to D from Frenkel, J. K., *The Adrenal Cortex*, H. D. Moon, editor. Hoeber Medical Division, Harper & Row, Publisher, 1961.)

gin) itself secretes an ACTH-like substance, and the adrenals are large and apparently functional in spite of widespread replacement. Bilateral nonfunctioning adrenal carcinomas cause pressure atrophy of the functioning cortex, and so can pheochromocytomas.

4. Infarction necrosis. This is mainly of two types. It may follow thrombosis of the adrenal vein, usually unilateral, sometimes related to surgery in the area, but usually of unknown etiology. The other type results from gram negative bacterial infection with endotoxinemia, such as the ***Waterhouse-Friderichsen syndrome,*** where adrenocortical thrombosis and resultant hemorrhage is often widespread. Such patients who do not succumb to acute infection and intoxication will occasionally later on exhibit adrenocortical insufficiency, followed by gradual recovery as compensatory hyperplasia is achieved. Pathogenesis is complex, but appears related to the generalized Shwartzman phenomenon.[59] Fibrin thrombi have been demonstrated in the adrenocortical sinusoids of certain cases, and it was postulated that total involvement of the adrenal by hemorrhage resulted from confluent infarction. In what proportion of instances of Waterhouse-Friderichsen syndrome this sequence is operative remains unclear, as thrombi are often seen only in the less destroyed areas, suggesting that fibrinolysis may have removed them in the more hemorrhagic areas. The mechanism of thrombosis in the Shwartzman phenomenon has been reviewed and analyzed by McKay.[60] It has been demonstrated that the generalized Shwartzman reaction can be elicited in cortisone-treated rabbits without preparatory injection of endotoxin.[61] It has been suggested therefore, that precipitation of fibrin aggregates in the adrenals (rather than in the kidneys as in hypercorticoid rabbits) may result from the potentiating effects of the high corticosteroid level present.[40] Regardless of the mechanism of adrenal tissue destruction, most investigators now agree that the profound shock of Waterhouse-Friderichsen syndrome is not due to corticoid deficiency but to the overwhelming toxemia which accompanies the syndrome.

The shock which develops in this syndrome occurs much too rapidly to allow for depletion of the circulating corticoids. However, if the patient survives for more than a day, corticoid deficiency may complicate the picture and replacement therapy is indicated.

5. Amyloidosis. Deposits of amyloid in the adrenals are sometimes part of the generalized "secondary" amyloidosis. However, the deposits in the adrenals may be more extensive than in other body organs thus causing (or following) more complete destruction of them. Reports conflict concerning the potentiating or inhibitory effects of corticosteroids in amyloidosis.

6. Adrenal hemorrhage (Waterhouse-Friderichsen syndrome). Adrenal hemorrhage has been observed after septicemic bacterial infections, especially with meningococci and gram negative rods (Fig. 9.19). In addition there have been numerous instances after extensive burns, trauma, gastrointestinal surgery and a variety of other diseases, where disseminated infection with gram negative bacteria and release of their endotoxin was likely, although not always demonstrated. Adrenal hemorrhage was found in 22 of 40 autopsies[59] on patients with meningococcemia and in 14 of 47 of another series.[62] Hemorrhage may be generalized or patchy; it starts in the zona reticularis and progresses outward. The parenchyma may be almost completely destroyed. However, in a series of patients, peripheral blood corticosteroid levels were found to be above normal, consistent with previous adrenal hyperactivity and insufficient lapse of time for decay of the corticosteroid level.[63] In patients surviving a clinical course similar to that which was fatal, complete recovery was the rule, although sometimes following an interval with manifestations of hypocorticism, relieved by replacement therapy. Judging from evidence, such as Skelton's[64] concerning regeneration of the adrenal after removal of all but the subcapsular cells, regeneration after subtotal hemorrhagic destruction in man would not appear impossible.

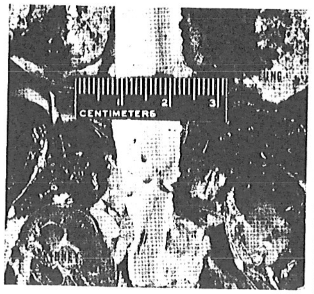


FIG. 9.19. Bilateral adrenocortical hemorrhage (Waterhouse-Friderichsen syndrome) viewed from the rear. Note the petechial hemorrhages of all organs and necrosis of both adrenals (*arrows*). (Courtesy Dr. David Jenkins.)

An important associated finding is ***pseudotubular degeneration,*** principally in the zona glomerulosa, which may also be present as sole finding in meningococcemia. It is also common in a variety of disease states where "stress" may reasonably be expected to have occurred. Wilbur and Rich[65] have shown that in rats cytolysis resulted in pseudotubular degeneration after intense stimulation with ACTH. In fatal diphtheria of man, human pseudotubular degeneration is the rule, sometimes associated with hemorrhage. This lesion has been studied experimentally by Tonutti[66] in guinea pigs who found that it resulted from the action of the exotoxin in an intensely functional adrenal.

The cause of adrenal hemorrhage is still being debated. The view used to be prevalent that the bacteria or endotoxin attacked the endothelium directly; however, specific staining for bacteria does not reveal a greater concentration of organisms in these adrenals than elsewhere in the same patient. In view of lipoid depletion and presence of pseudotubular degeneration, some suspected that impairment of the structural integrity of the sinusoidal lining gave rise to the hemorrhage. This appears unlikely as the hemorrhage starts in the reticularis, while pseudotubular degeneration is most marked in the zona glomerulosa.

The hypothesis of Margaretten and McAdams[59] equating all the hemorrhagic phenomenon of meningococcemia with the Shwartzman reaction has been mentioned in the discussion of infarction necrosis. Also, the additional postulate that the adrenal was uniquely predisposed to the precipitation of the Shwartzman fibrin aggregates on account of its high concentration of corticosteroids. However, the infrequency of actual demonstration of fibrin thrombi in the adrenocortical sinusoids raises doubt on the frequency with which this mechanism is operative.

Recently Levin and Cluff[67] produced adrenal hemorrhage in rabbits injected twice with endotoxin, or with thorotrast or ACTH, followed by endotoxin at 4-hour intervals. The Shwartzman reaction did not occur in the kidney till the interval was increased to 10 hours. That the adrenal hemorrhage was independent of intravascular clotting was shown by the injection of heparin, which although modifying the Shwartzman reaction, did not impair the occurrence of adrenal hemorrhage. The need for an active adrenal was demonstrated when thorotrast or ACTH-pretreated rabbits were pretreated for 1 week with cortisone acetate and cortisol, which "markedly" suppressed adrenal hemorrhage after endotoxin was administered. These authors found that nitrogen mustard-induced granulocytopenia mitigated, however, both the effect of endotoxin on the adrenal cortex and the Shwartzman phenomenon, suggesting the participation of released lysosomal enzymes in both types of tissue damage. The close interval between sensitizing and precipitating injection in the experimental model parallels the short interval after onset of the disease and the fatal Waterhouse-Friderichsen syndrome, which does not usually develop after 48 hours from the onset of disease.[56] Although in these experimental models adrenal lesions were not studied for their dependence on the two types of steroids (compounds B & F) as could have been done by the use of Metapirone. Although the degree of adrenal unresponsiveness after corticosteroid pretreatment was indeterminate, these experiments provided a new approach to the explanation of this baffling problem.

Cushing's Disease

Since Cushing's original report[68] in 1932 there has been dispute about the etiology of the disorder bearing his name. He considered a small basophilic pituitary adenoma to be the cause. The findings today include: truncal obesity, red "moon face" with acne, "buffalo hump" shoulder fat pads, abdominal striae, thin skin, thin arms and legs, easy bruisability, muscle wasting, poor wound healing, hypertension, hyperglycemia, polycythemia, osteoporosis and an increased excretion of cortisol and other adrenocortical hormone derivatives. In females cessation of menses and hirsutism may be added. When these findings exist in the presence of a pituitary adenoma some call it ***"Cushing's disease."*** With availability of cortisol the complete "disease" has been iatrogenically produced by hormones from a bottle so there can be no doubt that the natural disease is mediated by the adrenal cortex. When the disorder occurs without anatomical findings of an adenoma in the pituitary some use the term ***"Cushing's syndrome."***

When there is excess ACTH in the plasma there will be diffuse uniform hypertrophy and/or hyperplasia of both adrenals. Cushing's disorder may or may not be present. It appears that there may be two or more kinds of ACTH, *viz.*, an adrenal weight-maintaining factor and the usual steroid-forming and steroid-releasing factor. Such a concept is required to explain the bilaterally large adrenals frequently found at autopsy when Cushing's disorder is not clinically present. Such adrenals, each weighing 10 to 15 g. are frequently found in cases of lung tumors.[69] It is obvious that these large adrenals must be partially refractory to ACTH, or the usual ACTH must be decreased in the plasma, otherwise Cushing's disorder would appear. That is to say if adrenal cortical tissue continued to secrete cortisol at its usual rate after it had hypertrophied to twice the normal mass then the glands would be secreting cortisol at twice the normal rate and Cushing's disorder would ensue. Since some patients with very large adrenals do not have Cushing's disorder it is, therefore, obvious that some large adrenals may be inefficient glands or glands working at a low basal rate. The latter probably prevails because many patients with carcinoma of the lung, but without Cushing's disorder, hyperrespond to test doses of ACTH and subsequently, at autopsy, are found to have very large adrenals.[64, 69 72] Nonpituitary ACTH-producing tumors are further discussed in Chapter 19.

With hypertrophy or hyperplasia of both glands the clinical effects of Cushing's disorder may be ameliorated by complete removal of one gland and the major portion of the alternate gland. However the remaining fragment will regenerate and the clinical condition usually reappears. When both adrenals are completely removed the disease abates unless there is ectopic tissue. In an alarming number of patients with bilateral adrenalectomy a basophilic or chromophobic adenoma arises in the pituitary a few years later. These patients usually show profound pigmentation from excessive ACTH and melanocyte-stimulating hormone secretion of the pituitary and/or its tumor. Of course the question arises: "Were not these pituitary tumors present in the first instance?" If so, then adrenalectomy unmasks latent growth potential of these tumors the growth of which may be inhibited by cortisol and the normal spectrum of adrenal hormones. Another possibility is that following removal of most or all of the adrenal tissue, the pituitary cells are under excessive stimulus from the hypothalamus to produce ACTH despite replacement therapy, which may not be sufficient. As a result there is an ultimate breakaway from normal body control and the initiation of a true neoplasm.

In the event one gland contains an adenoma it may be "an incidental nonfunctioning adrenocortical adenoma" if the alternate gland is apparently normal or hyperplastic. However if the alternate gland and the uninvolved portion of the gland containing the adenoma are atrophic with sharp edges then the adenoma is probably functioning and removal may effect a "cure." Microscopic examination of the adrenal tissue may be unrewarding and the histologic appearance may be entirely normal. It seems possible and probable that functioning and nonfunctioning adenomas may exist side by side in the same and/or contralateral glands and yet may not be identified by the usual microscopic study. However, if one does exhaustive nuclear size studies as indicated by Holley[32] the cell nuclei in the hyperfunctioning tissue will be found large and in the hypofunctioning tissue they will be small.

The microscopic appearance of bilaterally diffusely enlarged adrenals which cause Cushing's disorder is quite variable. Within the same gland there may be fields of normal cortex alternating with distinctly abnormal fields containing markedly hypertrophied cells with lipids, similarly enlarged cells with hydropic cytoplasm, a few scattered dark compact cells and a few lymphocytes. There may be considerable variation in size, shape and position of the nuclei. The reticular framework of these hyperplastic fields does not have the regular pattern expected of any normal zone. In some places the cells may be arranged in a haphazard fashion; in other areas they may assume an adenomatous pattern apparent only by examination with the microscope, and characteristically encompassed by a delicate band of compressed reticular tissue. Fresh hemorrhage may be present in any place when it is a surgical specimen. This is due to operative trauma and clamping the venous drainage before all of the arterial supply is occluded. When necrosis is present, no matter how small and focal, malignancy must be strongly suspected.

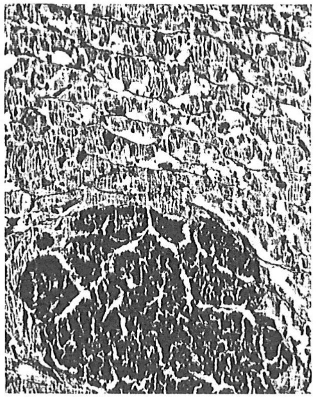


FIG. 9.20. Photomicrograph of adrenal cortex in a case of anaplastic adrenocorticotropic hormone-secreting carcinoma of lung. Note the profound enlargement of the cortical cells the cytoplasm of which is devoid of lipids and stains poorly. The cluster of small, dark anaplastic cells at the bottom of the figure compressing the surrounding parenchyma is a metastasis from the lung tumor. H&E, 112×.

Figure 9.20 is from a diffusely hypertrophied and hyperplastic adrenal in a case of lung carcinoma. Cushing's syndrome was of sudden onset with profound hypokalemic alkalosis and death ensued within 6 weeks. An ACTH-like protein was extracted from the primary tumor. The alkalosis, rapid course, and severe intensity of symptoms are characteristic of ACTH-producing nonendocrine tumors. The right adrenal weighed 28 g. and the left 32 g. The cluster of small hyperchromatic anaplastic cells, seen in the figure, are metastatic from the lung. The metastatic nodule may have secreted ACTH but did not seem to have a local effect. It appeared to be growing faster than the adrenal parenchyma and compressed the adjacent cortical cells. The cortical parenchyma composed mainly of markedly hypertrophied cells devoid of lipid has a cytoplasm which stains poorly. Only a very few lipid-containing cells are present as vacuoles and there are a few compact cells. These microscopic findings are uniform in all sections of both glands studied and also characterized three other pairs of adrenals from cases of ectopic ACTH-like secreting nonendocrine tumors studied by the writer. In cases where the ACTH arises from carcinomas of the lung, thymus, thyroid, pancreas, ovary, parotid and prostate the bilateral adrenal hypertrophy is usually greater than that which occurs when the ACTH arises from the pituitary.

In borderline cases Cushing's syndrome may be diagnosed by finding that the diurnal variation in plasma 17-hydroxycorticosteroids have disappeared and that the plasma level fails to suppress below 5 μg. at 8 a.m. following administration of 1 mg. of dexamethasone at 11 p.m. the previous night. Differentiation between hyperplasia and an autonomous tumor may be made by giving an infusion of 30 to 60 mg. per kg. Metapirone over a 4-hour period. Patients with normal and hyperplastic adrenals will show a marked increase (usually two times) in 17-hydroxycorticosteroid output in the urine. Patients having tumors independent of the pituitary will not show this effect. Somewhat the same result may be achieved by the dexamethasone suppression test in which 8 mg. per day are given for 4 days. If the adrenal is hyperplastic the 17-hydroxycorticosteroids in the urine will be markedly reduced but if the patient has a tumor independent of ACTH no effect will be observed. Also ACTH may be administered to the patient intravenously. If the tumor is a benign adenoma an excessive response is frequently obtained whereas if the tumor is malignant a response is usually not obtained. It may be said, in general, that pituitary-dependent tumors or hyperplasias produce mainly an excessive amount of cortisol while malignant tumors produce a wider spectrum of hormones including especially androgenic substances.

MISCELLANEOUS

The adrenal cortex may be involved in a wide variety of pathologic processes of varying degrees of importance. For example, inclusion bodies are frequently found in the cortical cells in several viral conditions. A most striking example is the adrenal of Figure 9.21. The patient had been delivered by cesarean section 9 days previously from a mother who had herpes simplex lesions on the lips and labia. At autopsy the infant had extensive esophagitis and massive liver involvement in addition to necrosis of both adrenals. The fetal zone of the adrenal was absent and most of the definitive zone was necrotic. In the "viable" areas the nuclei can be seen to contain typical inclusion bodies (Fig. 9.22). Apparently the virus reached the infant across the placenta and had been present for some time in order to destroy the fetal cortex.

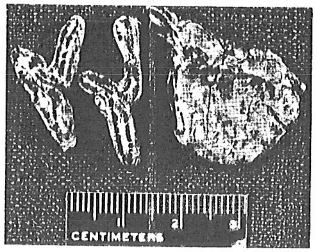


FIG. 9.21. Adrenal from a fatal case of herpes simplex. Girl age 9 days born by cesarean section. The infant also had esophagitis and massive liver involvement. The fetal zone of the adrenal is completely necrotic and the remainder of the cortex shows extensive patchy necrosis. (Courtesy of Dr. Thomas DeFeo.)

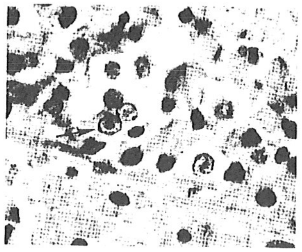


FIG. 9.22. Photomicrograph of an apparently viable (by naked eye) area of cortex in Figure 9.21. Many of the naked nuclei have inclusion bodies (*arrow*). Other nuclei show margination and clumping of chromatin. Herpes simplex virus was grown from the infant's liver. H&E, 475×.

Some miscellaneous conditions worthy of mention include cytomegalic cells of the fetal cortex,[73] hemorrhage during delivery, cysts,[74] myelolipomatous change,[76] hemangiomas, atrophy in Schilder's disease,[76] hemorrhagic infarcts from pyrogens,[86] etc.

A few words may be said about therapy of adrenocortical carcinoma. Of the many attempts at therapy only a few have had any effect. Amphenone [3,3-di(p-aminophenyl)butanone-2-dihydrochloride] inhibits many features of adrenocortical carcinoma but has been abandoned because of toxicity.[79] The isomers of DDD[2,2-bis(chlorophenyl)-1,1-dichloroethane] and many of its analogs have varying capacities to inhibit the adrenal cortex but again they have considerable toxic effects. The biologic effects of some of these have been reviewed[78] as have been the clinical effects.[79] It is too early to judge the effects of aminoglutethimide,[80] and DL-2(p-Aminophenyl)-2-phenylethylaminine.[87]

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